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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/676,718 | 09/28/2000 | Vadim N. Gladyshev | 4239-56113 | 1779 |

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| EXAMINER | |
|---|---|
| RAWLINGS, STEPHEN L | |
| **ART UNIT** | **PAPER NUMBER** |
| 1642 | 18 |

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/676,718 | GLADYSHEV ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *51-53,64 and 67-83* is/are pending in the application.

4a) Of the above claim(s) *78 and 79* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-53,64, 67-77, and 80-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *14*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendment filed September 2, 2003 is acknowledged and has been entered. Claims 55, 60, 63, and 66 have been canceled. Claims 51, 52, 64, and 82 have been amended. Claim 83 has been added.

2. Claims 51-53, 64, and 67-82 are pending in the application. Claims 78 and 79 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12.

3. Claims 51-53, 64, 67-77, and 80-83 are currently subject to examination.

### *Grounds of Objection and Rejection Withdrawn*

4. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed April 9, 2003 have been withdrawn.

### *Response to Amendment*

5. For clarity of record, the listing of the claims set forth in the amendment filed September 2, 2003 does not correctly list the status of claims 78 and 79. Claims 78 and 79 have been withdrawn from further consideration as noted above. Although the amendment is not entirely compliant with the current amendment practice set forth under 37 CFR § 1.121, in the interest of advancing prosecution the deficiency has been overlooked with the understanding the amendment does not correctly list the status of claims 78 and 79 as withdrawn.

In addition, Applicant's remarks at page 8, paragraphs 4 and 5 are acknowledged. Applicant has remarked it was agreed during the telephonic interview of August 29, 2003, this amendment would overcome the 35 USC § 112, first and second paragraph rejections of claim 51, provided Applicant could demonstrate where in the specification support for such an amendment could be found. During the telephonic

interview with Applicant's representative, Dr. Rybak, on August 29, 2003, the Examiner addressed Dr. Rybak's query as to whether proposed amendments to the claims might be sufficient to obviate the stated grounds of rejection under 35 USC § 112, first and second paragraphs. It was agreed that the new matter rejection set forth in section 9 of the Office action mailed April 9, 2003 would be overcome if Applicant were to point to specific disclosures in the specification that provide proper and sufficient written support for the language of the rejected claims, or otherwise if Applicant were to amend the claims in a manner, which finds such written support in the specification, as originally filed. It was further agreed that if claim 51 were amended to be drawn to a method for determining if a subject has a cancer, rather than if a subject has an increased risk of developing cancer, then the rejection set forth under 35 USC § 112, second paragraph in section 13 of the Office action would be rendered moot. Regarding the written description rejection set forth in section 10 of the Office action, it was agreed that if claim 51 were to be amended to recite a limitation that the members of the genus of 15 kDa selenoproteins have a particular function, the presence of which correlates with the recited structural features of those members, then the written description requirement set forth under 35 USC § 112, first paragraph would be met. Regarding the enablement rejection set forth in section 11 of the Office action, if claim 51 were amended to be drawn to a method for determining if a subject has a cancer comprising determining the amount of the polypeptide of SEQ ID NO: 4, and said cancer were limited to the specifically disclosed types of cancer, which Applicant has described as being characterized by the relative under-expression of the polypeptide of SEQ ID NO: 4, namely prostate cancer, ovarian cancer, fallopian tube cancer, liver cancer, and lymphoma, the Examiner agreed to carefully consider whether the enablement requirement set forth under 35 USC § 112, first paragraph would then be met. Finally, although the above-described agreements were made, it was agreed that the Interview Summary would merely reflect the fact that Applicant's representative and the Examiner discussed whether the proposed amendments would obviate the grounds of rejection set forth in the previous Office action; see Paper No. 14.

***Claim Rejections - 35 USC § 112***

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 82 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 82 is drawn to the method of claim 51 wherein the cell of the subject is a lymph node cell. At page 19, lines 7-9, the specification discloses Northern blot analysis revealed reduced expression of the 15 kDa selenoprotein in lymphoma relative to normal lymph node. However, this disclosure does not provide written support for the method of claim 51 wherein the cell of the subject is a lymph node cell, because in context, "the cell of the subject" is a lymphoma cell, while the "control cell" is a lymph node cell. A lymph node is an organ composed of a loose network of reticular tissue in which are enmeshed large numbers of lymphocytes, macrophages, and accessory cells; a lymph node is therefore composed of a variety of cell types. In contrast, a lymphoma is a malignant tumor of lymphoblasts derived from B-lymphocytes. Accordingly, a lymph node may comprise a lymphoma cell, but a lymph node cell is not necessarily a lymphoma cell. Thus, while the disclosure at page 19 would provide written support for limiting "the cell of the subject" to a lymphoma cell, it fails to provide proper and sufficient written support for limiting "the cell of the subject" to a lymph node cell.

This issue might be resolved if Applicant were to point to specific disclosures that are believed to provide the necessary written support.

8. Claims 51-53, 64, 67-77, and 80-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The present claims are drawn to a method comprising measuring the expression of a genus of mammalian 15 kDa selenoproteins comprising an amino acid sequence having at least 95% identity to SEQ ID NO: 1, rather than at least 70% identity. However, the written description requirement is still not met by the specification, because as set forth in the previous Office action, the specification only provides an adequate description of the polypeptide of SEQ ID NO: 1 and fails to disclose how the polypeptide of SEQ ID NO: 1 is to be regarded as representative of the genus of polypeptides to which the claims refer.

Applicant has traversed this ground of rejection arguing the following:

(a) The specification describes how one skilled in the art can make substitutions in SEQ ID NO: 4.

(b) The skilled artisan could instantly envisage several members of the genus of mammalian 15 kDa selenoproteins to which the claims are drawn, because one could instantly envisage proteins comprising an amino acid sequence, which is at least 95% identical to SEQ ID NO: 4.

(c) Because the specification describes and compares the amino acids sequences of proteins isolated from mouse, rice, and nematode, which are homologous to the amino acid sequence of SEQ ID NO: 4, the skilled artisan would amino acids are conserved. As conserved amino acids are important to the function, the specification discloses which amino acids may be substituted, and which may not be, without substantial loss of function.

In addition, Applicant has stated that the scope of the claims is not intended to encompass other non-15 kDa selenoproteins, but is intended to encompass selenoproteins, which are encoded by naturally occurring allelic variants of the gene encoding the polypeptide of SEQ ID NO: 4.

Applicant's arguments and remarks have been carefully considered but not found persuasive for the following reasons:

(a) Although the specification describes how one skilled in the art can make substitutions in SEQ ID NO: 4, according to MPEP § 2163.02, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". Furthermore, the courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Therefore, contrary to Applicant's assertion, to meet the written description requirement, the disclosure must do more than merely describe a means for making and using the invention.

(b) Although the skilled artisan could instantly envisage at least a substantial number, if not all, of the proteins consisting of an amino acid sequence that is at least 95% identical to SEQ ID NO: 4, the skilled artisan could not immediately recognize or distinguish those proteins, which are members of the genus of mammalian 15 kDa selenoproteins to which the claims refer, because the specification fails to describe a functional attribute shared by at least a substantial number of the members of the genus, which correlates with the presence of the recited structural feature also common to those members. In other words, although every member of the claimed genus of proteins necessarily has an amino acid sequence that is at least 95% identical to SEQ ID NO: 4, the skilled artisan could not recognize or distinguish the members of the genus from other proteins commonly having an amino acid sequence that is at least 95% identical to SEQ ID NO: 4, but which differ functionally. In fact, the specific function of the polypeptide of SEQ ID NO: 4 is not disclosed, so the skilled artisan could not distinguish members of the genus of selenoproteins to which the claims refer by functional assay; and as evidenced by the teachings of Skolnick et al. it would be unreasonable to presume that any protein comprising an amino acid sequence that is merely 95% identical to the amino acid sequence of SEQ ID NO: 4, but which does not

necessarily share the function of the polypeptide of SEQ ID NO: 4 is under-expressed in cancer cells, simply because Applicant discloses the polypeptide of SEQ ID NO: 4 is under-expressed in certain cancer cells as compared to cells of the same tissue type.

(c) Conserved amino acids are generally important to the function of an evolutionarily conserved protein and its homologs, *provided* the protein and its homologs share the same function. However, the specification does not disclose the specific function of the polypeptide of SEQ ID NO: 4, or the whether its function is conserved by evolutionarily related homologs thereof. Because rice, for example, does not develop cancer, as do mammals, it could not be reasonably construed that the rice homolog of the polypeptide of SEQ ID NO: 4 would be commonly associated with abnormal levels of expression in cells having a transformed or malignant phenotype simply because the proteins share regions of evolutionarily conserved amino acids. Moreover, while the amino acid sequences of the polypeptide of SEQ ID NO: 4 and its described rice, mouse, and nematode homologs have evolutionarily conserved regions, the specification fails to describe any correlation between the presence of these conserved regions and any particular function, or any association with abnormal levels of expression in cells having a transformed or malignant phenotype. Contrary to Applicant's assertion, the specification cannot have disclosed which amino acids may be substituted, and which may not be, without substantial loss of function or association, because the specification fails to describe the function of the protein, which is necessarily retained by the variants or homologs of the polypeptide of SEQ ID NO: 4, or the specific structural attributes of the protein, which is necessarily retained by the variants or homologs of the polypeptide of SEQ ID NO: 4 associated with abnormal levels of expression in cells having a transformed or malignant phenotype.

In reply to Applicant's remark, the scope of the claims is not intended to encompass other non-15 kDa selenoproteins, but is intended to encompass selenoproteins, which are encoded by naturally occurring allelic variants of the gene encoding the polypeptide of SEQ ID NO: 4, the claims are specifically drawn to mammalian 15 kDa selenoproteins, so it agreed the claims do not encompass non-15 kDa selenoproteins. To the extent claim 51 is drawn to a method comprising measuring

the amount of 15 kDa selenoproteins, which have an amino acid that is at least 95% identical to SEQ ID NO: 4, it is agreed the scope of the claims includes any described and yet to be described 15 kDa selenoprotein encoded by an allelic variant of the gene encoding the polypeptide of SEQ ID NO: 4, provided the other protein has an amino acid that is at least 95% identical to SEQ ID NO: 4. The specification has not described any naturally occurring variant of the polypeptide of SEQ ID NO: 4, which is encoded by an allelic variant of the gene encoding the polypeptide of SEQ ID NO: 4; although the specification does describe allelic variants, the variants are not disclosed as encoding proteins that differ from the polypeptide of SEQ ID NO: 4, because the polymorphisms described appear in the 3' untranslated portion of the cloned nucleic acid molecules. Nevertheless, it is currently Office practice not to reject claims merely encompassing possible allelic variants, where such allelic variants have not been described so as to meet the requirements set forth under 35 USC § 112, first paragraph, unless the claims specifically refer to those allelic variants.

In summary, although Applicant's arguments and remarks have been carefully considered, the written description requirement set forth under 35 USC § 112, first paragraph has not been met by Applicant's disclosure of the claimed invention, because the polypeptide of SEQ ID NO: 4 is not deemed representative of the genus of mammalian 15 kDa selenoproteins to which the claim 51 refers, as even given benefit of the disclosure, the skilled artisan could not immediately recognize or distinguish those members from other proteins having amino acid sequences that are at least 95% identical to SEQ ID NO: 4. To meet the written description requirement, the disclosure must include a description of at least a substantial, or at least a representative number of embodiments encompassed by the claims, and must be of sufficient detail to satisfy a factual inquiry to determine whether the skilled artisan would have reasonable cause given only benefit of Applicants original disclosure, to accept the assertion set forth in the claims that Applicants had possession of the claimed invention as of the filing date sought. The present disclosure does not include a description of at least a substantial number of embodiments of the methods encompassed by the claims; nor does it include

a description of at least a representative number of embodiments of the methods encompassed by the claims.

9. Claims 51-53, 64, 67-77, and 80-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using a method for determining if a subject has prostate cancer, ovarian cancer, fallopian tube cancer, or lymphoma, wherein said method comprises determining if a suspect prostate cell, ovarian cell, fallopian tube cell, or a B-lymphoblast of the subject has a reduced amount of the 15 kDa selenoprotein of SEQ ID NO: 4, or a reduced amount of a nucleic acid molecule encoding said protein, as compared to a normal cell of the same type, does not reasonably provide enablement for using a method for determining if a subject has cancer comprising determining if a cell of the subject has a reduced amount of a mammalian 15 kDa selenoprotein having an amino acid sequence that is at least 95% identical to SEQ ID NO: 4, or a reduced amount of a nucleic acid molecule encoding said protein, as compared to a control cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The present claims are drawn to a method for determining if a subject has a cancer, rather than a method for determining if a subject has an increased risk of developing a cancer, which was the claimed subject matter considered in the previous Office action.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein is insufficient to enable the skilled artisan to have a reasonable expectation of successfully using the claimed invention without need of performing an additional, and undue amount of experimentation. The factors that have been considered in determining that undue experimentation would be required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of

working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

Applicant has traversed the ground of rejection set forth in the previous Office action, as Applicant apparently envisioned that ground might be applied to a rejection of the present claims. Applicant has argued the disclosure fulfills the enablement requirement set forth under 35 USC § 112, first paragraph because given benefit of Applicant's disclosure, the skilled artisan would have a reasonable expectation of success in using the claimed invention to determine if a subject suffers from cancer. In support of this assertion, Applicant has remarked the specification discloses *in vivo* data that was acquired using samples obtained from a live organism or from tissue culture cells, which Applicant argues shows the expression of a 15 kDa selenoprotein is decreased in cancer cells relative to normal cells. In particular, Applicant has referred to the disclosures at page 18, line 14, to page 19, line 9, of the specification.

Applicant's arguments and remarks have been carefully considered but not found persuasive for the following reasons:

As established by the previous Office action, the art is highly unpredictable, as it would be unreasonable to expect a characteristic feature of one type of cancer to be common among any other type of cancer, absent factual evidence otherwise wrought by empirical determination. Accordingly, one skilled in the art cannot predict whether the polypeptide of SEQ ID NO: 4 or any other polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 4 will be under-expressed in any and all types of cancer, as compared to a control cell. Moreover, one skilled in the art cannot predict whether the relative under-expression of any such polypeptide by a cell is so characteristic of cancer that it can be used as an indication that the cell is cancerous. It is well appreciated that a universal tumor marker has been yet to be discovered and characterized. As such, although Applicant discloses that the amount of the protein of SEQ ID NO: 4, or a nucleic acid molecule encoding the protein is reduced in certain cancer cells, the skilled artisan would not accept the assertion that the protein or any

other protein having an amino acid sequence that is at least 95% identical to SEQ ID NO: 4 is under-expressed in any and all types of cancer.

In addition to the teachings of Ward and others cited in the previous Office action as support for the Office's position, Applicant's disclosure provides factual evidence the skilled artisan could not have a reasonable expectation of successfully using the claimed invention to determine if a subject has any and all types of cancer. At pages 18 and 19, Applicant discloses Northern blot analyses revealed the amount of a messenger RNA (mRNA) molecule encoding the polypeptide of SEQ ID NO: 4 is reduced in lymphoma and ovarian and fallopian tube cancer, as compared to matched normal control cells of the same organ. In addition, Applicant discloses Western blot analyses revealed the amount of the polypeptide of SEQ ID NO: 4 is reduced in prostate cancer cell lines, as compared to normal prostate. While similar analyses revealed the relative under-expression of the mouse homolog of the polypeptide of SEQ ID NO: 4 in hepatocarcinomas of c-myc/TGF-α transgenic mice, Applicants disclose at page 18, lines 35-37, the amount of the polypeptide in the hepatocarcinomas of c-myc and c-myc/TGF-β transgenic mice *is not altered*. Thus, Applicant's disclosure provides factual evidence the skilled artisan could not have a reasonable expectation of successfully using the claimed invention to determine if a subject has any type of hepatocarcinoma, because it appears that the relative under-expression the 15 kDa selenoprotein is not a general characteristic of hepatocarcinomas, but rather of only a very particular subset of hepatocarcinomas, which arise spontaneously in transgenic mice over-expressing c-myc and TGF-α. Because the expression of the 15 kDa selenoprotein in hepatocarcinomas of c-myc and c-myc/TGF-β transgenic mice is not reduced, compared to normal liver cells, Applicant's disclosure that the expression of the mouse homolog of the polypeptide of SEQ ID NO: 4 is reduced hepatocarcinomas of c-myc/TGF-α transgenic mice is not predictive of the success one might have in applying the claimed invention to the diagnosis of hepatocarcinoma in general, or of other forms of cancer, which have not been described as having reduced amounts of the 15 kDa selenoprotein or the transcript encoding the protein. Moreover, because it appears that

the invention may only be practiced with a reasonable expectation of success to determine if a subject has a cancer of a very particular etiology, it appears the amount of guidance and direction set forth by Applicant's disclosure would not be sufficient to enable the skilled artisan to practice the claimed invention in a manner that is reasonably commensurate in scope with the claims. Similar contrasting patterns of expression of other selenoproteins have been described by Gladyshev et al. (*Biochemical and Biophysical Research Communications* **251**: 488-493, 1998) in comparing cancers having different molecular etiologies, i.e., tumors caused by p53 mutation or the over-expression of c-myc and TGF-α, which suggests that the various members of the class of selenoproteins are not commonly expressed in any defined and characteristic manner in cancer, which is independent of its molecular etiology.

Further regarding the scope of enablement, Gladyshev et al. (*Journal of Biological Chemistry* 273: 8910-8915, 1998), teaches in Table II at page 8913, the mRNA encoding the human 15 kDa selenoprotein is *not* under-expressed in colon cancer relative to normal colon; in fact, to the contrary, Gladyshev et al. found the protein is over-expressed in colon cancer, since the complementary DNA (cDNA) clones encoding the protein in three cDNA libraries derived from mRNA present in colon carcinoma cells are over-represented relative to a cDNA library derived from mRNA present in normal colon. Accordingly, it appears the under-expression of the gene encoding the 15 kDa selenoprotein is not associated with colon cancer, so the claimed invention could not be practiced with a reasonable expectation of success to determine if a subject has colon cancer. Similar contrasting patterns of expression of other selenoproteins has been described by Gladyshev et al. (*Biochemical and Biophysical Research Communications* **251**: 488-493, 1998) in comparing different types of cancer, i.e., liver, prostate, and colon cancer, which suggests that the various members of the class of selenoproteins are not commonly expressed in any defined and characteristic manner in any and all types of cancer.

Applicant discloses at page 1, lines 17-19 of the specification, supplementation of the diet with selenium has been associated with a reduced incidence of prostate, colon, and lung cancer. While the biochemical basis for the protective effect of selenium in the

diet is unknown, Gladyshev et al. (*Biochemical and Biophysical Research Communications* **251**: 488-493, 1998) discloses a plausible hypothesis is that increased levels of selenium-containing proteins, which have antioxidant properties, are synthesized in response to increased levels of selenium in the diet. However, Gladyshev et al. teaches, "selenium appears to have a protective effect against some cancers, e.g., prostate, colon, and lung cancers, but not in others, e.g., skin cancer" (paragraph bridging pages 492 and 493). Since despite the protective effect of selenium against colon cancer, the expression of the 15 kDa selenoprotein is not reduced in colon cancer, the teachings of Gladyshev et al. (*Journal of Biological Chemistry* 273: 8910-8915, 1998) suggest an observation that selenium has protective effect against a cancer should *not* be taken as an indication that the claimed method might be practiced to determine if a subject has such a cancer. Nevertheless, the teachings of Gladyshev et al. (*Biochemical and Biophysical Research Communications* **251**: 488-493, 1998) might suggest that if selenium has no protective effect against a particular type of cancer, e.g., melanoma, then the presence of the cancer more likely than not could *not* be identified by the claimed method, because one would not expect the expression of the selenoproteins, including the 15 kDa selenoprotein to be abnormal in skin cancer and other types of cancer, since otherwise dietary selenium would been observed to be protective against such cancers, provided the hypothesis disclosed by Gladyshev et al. is correct. Thus, the combined teachings of Gladyshev et al. suggest that unless shown otherwise by exemplification, the skilled artisan would not have a reasonable expectation of success in practicing the claimed method in a manner that is reasonably commensurate in scope with the claims, because there is no reliable means of predicting whether or not a given type of cancer might be identified by practicing the claimed method.

It is noted that at page 11 of the amendment filed September 2, 2003, Applicant has stated the claimed invention can reasonably be expected to provide a means for determining if a subject has a cancer "related to decreased expression of a 15 kDa selenoprotein", as opposed presumably to just any type of cancer. While the claims are not so limited, it is not understood how the cancer would be "related" to the decreased

expression of a 15 kDa selenoprotein. Even so, Applicant's have not described the features that are characteristic of cancer having a decreased expression of a 15 kDa selenoprotein, such that skilled artisan would know which cancers can, or cannot be identified using the claimed method.

On a more technical note, as disclosed by Applicant in Table 2 at page 17 of the specification, Gladyshev et al. (*Journal of Biological Chemistry* 273: 8910-8915, 1998) teaches that several types of tissue or cells, e.g., germinal B-cells, express relatively little of the 15 kDa selenoprotein (Table II at page 8913). At page 491, column 2, Gladyshev et al. (*Biochemical and Biophysical Research Communications* **251**: 488-493, 1998) discloses that the low expression of most selenoproteins, including the 15 kDa selenoprotein *precluded* the reliable analysis of their expression levels. If certain types of cells express such low levels of the protein, e.g., it is reasonable to question whether the claimed method can be practiced with any reasonable expectation of success, because since the low levels of protein may preclude an analysis of those levels, it would not be possible to determine if the level of the protein is reduced even further in cancer cells of the same cell type. The specification does not appear to provide any guidance, direction, or exemplification, which might enable the skilled artisan to overcome these technical problems.

In summary, based upon preponderance of factual evidence of record, the amount of guidance, direction, and exemplification disclosed in the specification would not be sufficient to enable the skilled artisan to have a reasonable expectation of successfully using the scope of the claimed invention without need of performing an additional, and undue amount of experimentation.

***Conclusion***

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne (Bonnie) Eyler, Ph.D. can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1

slr
March 3, 2004